

The Vitamin D Newsletter

11/5/04

Interest in the upcoming NIH conference on cancer and vitamin D continues to build. Nicholas Zaminska of the Wall Street Journal is writing a story that should appear soon. We hope Zaminska's article will challenge cancer researchers to start thinking outside the box. All around the world, cancer patients are just dying to have scientists think outside the box. Maybe we'll see it in Bethesda. It's not too late to register. <http://vitamind.ucr.edu/Cancer%26CancerChemo.htm>

Dr. Reinhold Vieth, who helped start the current vitamin D revolution with a 1999 paper that challenged conventional views, will be at the conference. He certainly thinks outside the box. [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=10232622](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10232622)

Thinking outside the box always starts with simple questions like, "Why do humans make 20,000 units of vitamin D after just several minutes of sunshine?" The government says we only need a few hundred units a day. If we only need a few hundred, why did the species evolve a system that makes one hundred times that amount so very fast? For a good reason? What reason?

Another simple question is, "What is the rate limiting step for the production of calcitriol in the tissues?" That is, what prevents us from making too much calcitriol in our tissues? Although it sounds esoteric, this question may have profound implications for anyone suffering from cancer.

Remember, calcitriol is the most active metabolite of vitamin D. In fact, calcitriol is the most potent steroid hormone in the human body, active at 1/1,000,000,000,000 of a gram! In a way, the entire conference is about calcitriol and similar compounds because calcitriol appears to fight cancer in so many ways. It promotes apoptosis (normal cells die while cancer cells live on and on), it promotes differentiation (normal cells differentiate into specialized cells while cancer cells remain primitive), it prevents angiogenesis (blood vessels nourishing cancer cells), and it helps prevent metastasis. In short, calcitriol appears to be the perfect anticancer drug, at least in the test tube and in animal studies. Scientists have been trying to get high doses into the tissues of cancer patients for years. The problem is, up until now, no one has figured out a way to get calcitriol into the tissues without causing high blood calcium.

Fourteen years ago, Reinhold Vieth gave us a clue. He discovered that the production of calcitriol in the tissues is uncontrolled. Unlike other steroids, tissue calcitriol does not limit its own production; there is no negative feedback. Instead, the more 25(OH)D (calcidiol) in the tissues, the more calcitriol in the tissues! (Calcidiol is 25-hydroxy -vitamin D, which can easily be tested in the blood.) While calcitriol's lack of negative feedback over its own production may sound arcane, it gives us a clue to a steroid hormone system that is radically different from other steroids and that has profound implications for human health. [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=2185661](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=2185661)

Of course, the tissues degrade calcitriol, which results in lower tissue levels, but that does not limit calcitriol production in the first place. What is the rate-limiting step for the production of tissue calcitriol? Something has to control it. Perhaps the liver regulates calcidiol [25(OH)D] levels in the blood? No, the liver pumps out calcidiol into the blood almost as quickly as vitamin D comes in. That is, calcidiol production in the liver is also uncontrolled!

It looks as if the liver turns vitamin D into calcidiol as quickly as it can and the tissues turn calcidiol into calcitriol as quickly as they can. So far, each step is uncontrolled. Where can we find the rate-limiting step for the tissue production of this wondrous anticancer molecule, calcitriol?

Look at your arm. See your skin? Production of vitamin D in the skin is strictly limited. Your skin cannot make more than about 20,000 units of vitamin D a day. After awhile, the same ultraviolet light that first creates vitamin D in the skin begins to degrade it. The process achieves a steady state; production equals destruction.

Is it possible that your behavior is the rate limiting step for the tissue production of the most potent steroid hormone in the human body? If you regularly go into the sun, or take the right amount of vitamin D, your tissue calcitriol levels max out; if you assiduously avoid the sun, tissue calcitriol levels are minimal?

An important point to remember is that our kidneys have first dibs on any calcidiol hanging around. Calcidiol is not free to go to the tissues unless blood levels are high enough to get past the kidney. In a tightly controlled and crucial metabolic step, the kidneys snatch up calcidiol to regulate serum calcium levels. Any calcidiol left over from this endocrine function of vitamin D then goes to the tissues to produce tissue calcitriol.

What is the cut-off? That is, how can I be sure my tissues are getting all the calcitriol they need? Asked another way, how high do my calcidiol levels need to be, to be sure my kidneys can pass calcidiol on to my tissues? Actually, no one knows, but parathormone (PTH) levels give us a clue. When the kidneys don't get enough calcidiol, they signal the parathyroid to make more PTH. The parathyroid actually cranks out extra PTH until one reaches serum calcidiol levels of about 40 ng/ml, a level few of us achieve, and then the parathyroid slows way down. Further PTH suppression, although minimal, appears to occur at even higher calcidiol levels.

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list\\_uids=12519850](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12519850)

Think of it like the gas tank in your car. Humans have a vitamin D tank called blood calcidiol [25(OH)D]. Most of us only have a little calcidiol in the tank. Most of the calcidiol we do have goes to the kidneys to maintain serum calcium and keep us alive. However, if we'd just fill the tank, calcidiol would spill out into the tissues and enable us to make all the calcitriol our tissues desire. In evolutionary terms, humans have always had full tanks; only in the last several seconds of evolutionary time have our vitamin D tanks gotten so low we can't get calcidiol past the kidney and into the tissues.

It started when we migrated away from the equator 50,000 years ago. Then we industrialized and left the sun to work inside factories and live in cities, all of which deprived us of tissue calcitriol. Next, we started traveling in cars where glass blocks vitamin D production. Finally, we started listening to our doctors, lathering on the sunblock and hiding from the sun. In a mere second in evolutionary time, the human species went from about 20,000 units of vitamin D a day to less than 2,000 units and our tissue calcitriol levels plummeted.

Remember, the body tightly regulates all other steroids. Low levels ramp up production and high levels shut down production. But not vitamin D. Sun avoidance is just too new; humans have not had enough time to evolve a system to protect ourselves from low calcidiol levels, only high ones. Our species has yet to evolve a defense for a recent, and very radical, change in our behavior: sun-avoidance.

As Vieth has points out in the new edition of Feldman's, this leaves us with a quandary. Is it possible that modern humans have such low calcidiol levels that we have no way of knowing the natural state? That is, if high calcidiol blood levels helped diseases like cancer, we'd have no way of knowing it unless we thought outside the box.

[http://www.amazon.com/exec/obidos/tg/detail/-/0122526872/qid=1099704257/sr=1-1/ref=sr\\_1\\_1/104-7378072-2848769?v=glance](http://www.amazon.com/exec/obidos/tg/detail/-/0122526872/qid=1099704257/sr=1-1/ref=sr_1_1/104-7378072-2848769?v=glance)

One way to find out is to stop letting cancer patients die vitamin D deficient. Instead of letting them die with tiny amounts of calcidiol in their blood, why not give them the same amount of vitamin D as their ancestors always had. Of course, that would require thinking outside the box. Maybe the higher tissue calcitriol levels would help them fight their cancer, we don't know. It would certainly achieve something we've been trying to do for the last 20 years, raise tissue calcitriol levels in cancer patients.

Reinhold Vieth isn't the only one who thinks outside the box. Sometimes lawyers think outside the box. Many of them read the Wall Street Journal so they can invent out-of-the-box questions like, "Doctor, given

what science knows about calcitriol, why did you let Mrs. Jones die from cancer without even bothering to find out if she was vitamin D deficient?